Summary of the Examiner's Final Office Action

The Final Office Action dated April 5, 1999 contains the following issues requiring response:

(1) Rejection of claims 48-55 under Section 101;
(2) Rejection of Claims 27-31, 34-38, 40, 41, and 44-55 Under Section 112, First Paragraph;
(3) Rejection of Claims 44-47 and 51-55 Under Section 112, First Paragraph;
(4) Rejection of Claims 36-38 Under Section 112, Second Paragraph;
(5) Rejection of Claims 27, 28, 30, 31, 34-38, 41, and 48-50 Under Sections 102(b)/103(a);
(6) Rejection of Claims 27, 28, 30, 31, 34-36, 39-41, and 48-50 Under Sections 102(e)/103(a); and
(7) Rejection of Claims 36-38 and 50 Under Sections 102(e)/103(a).

Each of the issues raised by the Examiner is discussed below. Applicants believe that the foregoing amendment and the following remarks respond completely to the rejections. Applicants further believe the claims are in condition for allowance.

(1) Rejection of claims 48-55 under Section 101

Claims 48-55 stand rejected under 35 U.S.C. § 101, as directed to non-statutory subject matter. Claim 51-55 have been canceled without prejudice and claim 48 has been amended in the instant amendment. Claims 48-50 are pending in the instant application. Amended claim 48 recites a cultured mammalian cell infected with the replication defective recombinant adenovirus according to claim 27. Claims 49 and 50 depend directly or indirectly from amended claim 48. Applicants respectfully traverse the rejection and submit that the claims, as amended herein, are drawn to statutory subject matter. Accordingly, Applicants request respectfully that this rejection be reconsidered and withdrawn.

(2) Rejection of Claims 27-31, 34-38, 40, 41, and 44-55 Under Section 112, First Paragraph

Claims 27-31, 34-38, 40, 41, and 44-55 stand rejected under 35 U.S.C. § 112, first paragraph as not adequately described in the Specification. In particular, the Examiner has objected to the breadth of the claims with respect to glutathione peroxidase. The Examiner has also objected to the terms E1A, MLP, CMV, and RSV-LTR promoters. Applicants have canceled claims 28-31, 37, 44-47, and 51-55 without prejudice and have amended claims 27, 34, 36, 38, 40, 41, and 48 in the instant amendment. Claims 27, 34-36, 38, 40, 41, and 48-50 are pending in the instant application. Applicants respectfully traverse this rejection, and submit that the Specification contains a disclosure of the claimed invention which meets the requirements of 35 U.S.C. § 112, first paragraph.

Solely in an effort to advance prosecution, Applicants have amended independent claim 27 to recite a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase, essentially as suggested by the Examiner. Claims 34-36, 38, 40, 41, and 48-50 depend directly or indirectly from amended independent claim 27.

With regard to the Examiner's objection to the abbreviations used to designate promoters for use to control expression of the human glutathione peroxidase encoding cDNA sequence in the adenoviral vectors of the invention, Applicants submit that the abbreviations and corresponding structures of Applicants' disclosed E1A, MLP, CMV, and RSV-LTR promoters are well known and understood in the art. As evidence thereof, Applicants again direct the Examiner's attention to WO 94/08026, which was cited by the Examiner on PTO Form 892 and which corresponds to application PCT/EP93/02519 that was incorporated by reference in Applicants' Specification (see page 3, lines 6-10).

WO 94/08026, like the present application, is directed to gene therapy, particularly of disorders of the central nervous system using replication defective adenoviruses. WO 94/08026 constitutes subject matter known to those skilled in the art of the invention claimed herein. As discussed in Applicants' previous reply, mailed July 21, 1998, the terms MLP, CMV, and RSV-LTR are defined in this international application. Specifically, page 4, lines 18-19 defines MLP as the major late promoter of a human adenovirus. Similarly, RSV-LTR is defined as the Rous Sarcoma virus long terminal repeat (see page 4, lines 27-28 and page 10, lines 12-13). CMV represents a promoter derived from

cytomegalovirus (page 4, line 29). Applicants submit respectfully that WO 94/08026 is evidence that each of the terms MLP, CMV, and RSV-LTR would be readily understood by those skilled in the relevant art.

In addition, the Examiner has stated that the structure of the E1A promoter is evident from Applicants' Specification as being the endogenous adenoviral promoter of the E1a region (see page 7 of the Office Action, mailed January 21, 1998). Furthermore, the Examiner has stated that Applicants' previous arguments, which were set forth in the reply mailed July 21, 1998, convincingly demonstrate that one skilled in the adenoviral art would know what the abbreviations MLP, CMV, and RSV-LTR would mean in the context of the claimed invention (see page 5 of the Final Office Action, mailed August 31, 1998). Applicants respectfully submit that the abbreviations E1A, MLP, CMV, and RSV-LTR promoters are well known and understood by one of ordinary skill in the art.

Therefore, Applicants submit that one skilled in this art could, based on the disclosure within the Specification, make and use their invention as claimed. Accordingly, Applicants submit that claims 27, 34-36, 38, 40, 41, and 48-50 satisfy the written description requirements of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be reconsidered and withdrawn.

(3) Rejection of Claims 44-47 and 51-55 Under Section 112, First Paragraph

Claims 44-47 and 51-55 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 44-47 and 51-55 have been cancelled in the instant amendment. Therefore, the rejection is rendered moot by the instant amendment and should be withdrawn.

(4) Rejection of Claims 36-38 Under Section 112, Second Paragraph

Claims 36-38 stand rejected under 35 U.S.C. § 112, second paragraph. Claim 37 has been cancelled, without prejudice and solely in an effort to advance prosecution. Therefore, the rejection is moot with respect to this claim. Pending claims 36 and 38 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as their invention. Applicants respectfully traverse the rejection and submit that the claims are both

definite and clear and meet the requirements of 35 U.S.C. § 112, second paragraph.

Applicants believe that the terms E1A, MLP, CMV, and RSV-LTR are definite and clear, and would be readily understood by those skilled in the relevant art. As discussed above in Section 2, each of the terms E1A, MLP, CMV, and RSV-LTR are art recognized terms for promoters known to be useful in constructing replication defective adenoviral vectors, the subject matter of the claimed invention. WO 94/08026, which corresponds to application PCT/EP93/02519 that was incorporated by reference in Applicants' Specification (see page 3, lines 6-10), is evidence of this fact. As discussed above, WO 94/08026 clearly identifies the terms MLP, CMV, and RSV-LTR (see page 4, lines 18-28 and page 10, lines 12-13). Therefore, Applicants believe that the metes and bounds of the terms E1A, MLP, CMV, and RSV-LTR would be understood by the skilled artisan. Therefore, Applicants believe that further definition or clarification of these terms is unnecessary.

Applicants submit respectfully that claims 36 and 38 are both definite and clear and meet the requirements of 35 U.S.C. § 112, second paragraph. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(5) Rejection of Claims 27, 28, 30, 31, 34-38, 41, and 48-50 Under Sections 102(b)/103(a)

Claims 27, 28, 30, 31, 34-38, 41, and 48-50 stand rejected under 35 U.S.C. §§ 102(b)/103(a) as unpatentable over Kahn *et al.* in view of Mullenbach *et al.* Claims 28, 30, 31, and 37 have been cancelled without prejudice. Therefore, the rejection is moot with respect to these claims. Claims 27, 34, 36, 38, 41, and 48 have been amended in the instant amendment. Claims 27, 34-36, 38, 41, and 48-50 are pending in the instant application. Applicants respectfully traverse this rejection and submit that this combination of references in no way teaches or suggests Applicants' claimed invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Kahn *et al.*

Kahn *et al.* disclose replication defective adenoviruses for the transfer of genes into cells of the central nervous system. Kahn *et al.* disclose a number of genes encoding therapeutic molecules, which may be incorporated into the adenovirus, including antisense sequences, neurotransmitter synthesizing enzymes, growth factors, and neurotrophic factors (see pages 6 and 7).

Kahn *et al.* do not teach or suggest a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase.

Mullenbach *et al.*

Mullenbach *et al.* disclose the cDNA sequences for pituitary, kidney and placental glutathione peroxidases from bovine, human, and mouse sources, respectively (see page 313 and Figure 1). Mullenbach *et al.* is concerned with identifying the role of flanking and distant bases surrounding the single opal stop codon (UGA) that codes for the active selenocysteine residue in the glutathione peroxidase enzyme (see Abstract and pages 317-318).

Mullenbach *et al.* do not teach or suggest replication defective adenoviruses. Mullenbach *et al.* certainly do not teach or suggest a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase.

(b) Kahn *et al.* Do Not Render Obvious the Claimed Invention

Applicants' independent claim 27 has been amended in the instant amendment and defines a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase. Claims 34-36, 38, 41, and 48-50 depend directly or indirectly from amended independent claim 27. Kahn *et al.* neither teach nor suggest the invention defined by claim 27. The reference is deficient because it fails to teach or suggest a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase. Absent such a disclosure,

Kahn *et al.* cannot possibly render *prima facie* obvious the invention defined by Applicants' independent claim 27, or any of the claims dependent thereon.

(c) Mullenbach *et al.* do not correct the deficiencies of Kahn *et al.*

Mullenbach *et al.* is limited to a disclosure of cDNA sequences encoding various glutathione peroxidases and an analysis of the flanking and distant bases surrounding the single opal stop codon (UGA) that codes for the active selenocysteine residue in the glutathione peroxidase enzyme (see Abstract and pages 317-318). Mullenbach *et al.* fail to teach or suggest insertion of a human glutathione peroxidase encoding cDNA sequence into a replication defective adenovirus. Specifically, Mullenbach *et al.* fail to correct the deficiencies of Kahn *et al.*, because they do not provide one of ordinary skill in the art with either the suggestion or the motivation to insert a cDNA sequence encoding a human glutathione peroxidase into the replication defective recombinant adenovirus of Kahn *et al.* Absent such a disclosure, Mullenbach *et al.* cannot possibly correct the deficiencies of Kahn *et al.*

(d) The cited references fail to enable Applicants' claimed invention

Applicants respectfully submit that the Examiner is improperly picking and choosing from various teachings in the cited references in an effort to reconstruct Applicants' claimed invention. As discussed above, the prior art cited by the Examiner fails to teach or suggest Applicants' claimed invention. In this case, the primary reference Kahn *et al.*, fails to suggest a recombinant viral vector comprising a cDNA sequence encoding a human glutathione peroxidase. As discussed in Section (c) above, Mullenbach *et al.* fail to correct the deficiencies of Kahn *et al.* Mullenbach *et al.* suggest nothing beyond a nucleotide sequence encoding bovine, human, and mouse glutathione peroxidase. Indeed, nothing in the art cited by the Examiner teaches or suggests a recombinant viral vector comprising a cDNA sequence encoding a human glutathione peroxidase or cultured mammalian cells infected with such a recombinant viral vector, the subject matter of the claimed invention.

The burden of establishing a *prima facie* case of obviousness resides with the PTO. In re Piasecki, 223 USPQ 785, 788 (Fed. Cir. 1984) (quoting In re Warner, 154 USPQ 173, 177 (CCPA 1967)). However, nothing in the art cited by the Examiner teaches or suggests Applicants' claimed invention.

Specifically, neither of the cited references teach or suggest a replication defective recombinant adenovirus encoding human glutathione peroxidase. Applicants were the first to make this invention.

At best, the Examiner's position poses an "obvious to try" situation. However, the Federal Circuit Court has, on numerous occasions, noted that while something may be obvious to try, it may not be obvious under 35 U.S.C. ¤ 103. The proper standard is whether the prior art would have suggested to one of ordinary skill in the art that the invention should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. *In re Dow Chemical Company*, 5 USPQ 2d 1529, 1531 (Federal Circuit, 1988).

> Both the suggestion and the expectation of success must be founded in the prior art, not in Applicants' disclosure. Id.

In this case the cited combination of references simply does not suggest to one of ordinary skill in the art that Applicants' claimed invention could be achieved with a reasonable likelihood of success.

(e) The rejection is based on improper hindsight

As discussed above, the combination of Kahn *et al.* with Mullenbach *et al.* simply does not suggest to one of ordinary skill in the art that Applicants' claimed invention could be achieved with a reasonable likelihood of success. Mullenbach *et al.* fail to provide any instructions or motivation to substitute their disclosed human glutathione peroxidase cDNA sequence for the nucleotide sequences of Kahn *et al.* or to infect a cultured mammalian cell with such a replication defective recombinant adenovirus.

Applicants respectfully submit that they were the first to suggest the recombinant adenoviral vectors and cultured mammalian cells claimed herein, and to propose their use for methods of expressing a human glutathione peroxidase protein. Accordingly, the rejection must be based on improper hindsight given the benefit of Applicants' disclosure. However, use of hindsight reconstruction of an invention using Applicant's teachings is clearly improper, as has been stated by The Court of Appeals for the Federal Circuit on many occasions, see *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ at 312-313 (Federal Circuit, 1983) and *Interconnect Planning Corporation v. Feil, et al.*, 227 USPQ at 547 (Federal Circuit, 1985).

(f) Summary

Applicants submit respectfully that

1- Kahn *et al.* do not teach or suggest the claimed invention;
2- Mullenbach *et al.* fail to remedy the inherent deficiencies of Kahn *et al.*; and
3- the rejection is based on improper hindsight and "obvious to try" standards.

In this case, nothing in the art cited by the Examiner teaches or suggests a replication defective recombinant adenovirus comprising a cDNA seqeunce encoding a human glutathione peroxidase or a cultured mammalian cell infected with such an adenovirus. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn. Applicants submit that the combination of Kahn *et al.* with Mullenbach *et al.* fails to establish a *prima facie* case of obviousness against pending claims 27, 34-36, 38, 41, and 48-50. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(6) Rejection of Claims 27, 28, 30, 31, 34-36, 39-41, and 48-50 Under Sections 102(e)/103(a)

Claims 27, 28, 30, 31, 34-36, 39-41, and 48-50 stand rejected under 35 U.S.C. §§ 102(b)/103(a) as unpatentable over McClelland *et al.* in view of Mullenbach *et al.* Applicants respectfully remind the Examiner that claim 39 was cancelled in Applicants' previously submitted amendment and reply mailed July 21, 1998. Claims 28, 30, and 31 have been cancelled without prejudice in the instant amendment. Therefore, the rejection is moot with respect to these claims. Claims 27, 34, 36, 40, 41, and 48 have been amended in the instant amendment. Claims 27, 34-36, 40, 41, and 48-50 are pending in the instant application. Applicants respectfully traverse this rejection with respect to the remaining claims and submit that this combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

McClelland *et al.*

McClelland *et al.* disclose a modified adenovirus in which a portion of the viral fiber protein is replaced with a cell specific ligand. McClelland *et al.* teach that the adenovirus may also encode a therapeutic agent and provide a list of potential DNA sequences for insertion into the vector. Significantly, McClelland *et al.* neither teach nor suggest human glutathione peroxidase as a therapeutic agent. McClelland *et al.* certainly do not teach a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase, the subject matter of the claimed invention.

Mullenbach *et al.*

Mullenbach *et al.* fail to correct the deficiencies of McClelland *et al.* As discussed above in Section 5, Mullenbach *et al.* merely disclose the cDNA sequences for various glutathione peroxidases. However, Mullenbach *et al.* neither teach nor suggest replication defective recombinant adenoviruses. Mullenbach *et al.* certainly do not suggest a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase. Absent such a disclosure, the combination of McClelland *et al.* with Mullenbach *et al.* cannot possibly render *prima facie* obvious the invention defined by any of Applicants' claims.

As discussed above, the combination of McClelland *et al.* with Mullenbach *et al.* simply does not suggest to one of ordinary skill in the art that Applicants' claimed invention could be achieved with a reasonable likelihood of success. Mullenbach *et al.* fail to provide any instructions or motivation to substitute their disclosed human glutathione peroxidase cDNA sequence for the therapeutic agent of McClelland *et al.* or to infect a cultured mammalian cell with such a replication defective recombinant adenovirus.

Applicants submit that they were the first to suggest the replication defective recombinant adenoviruses and cultured mammalian cells claimed herein. As above, the combination of McClelland *et al.* with Mullenbach *et al.* is only possible using improper hindsight based on Applicants' disclosure. Accordingly, this rejection is untenable and should be withdrawn.

(7) Rejection of Claims 36-38 and 50 Under Sections 102(b)/103(a)

Claims 36-38 and 50 stand rejected under 35 U.S.C. §§ 102(b)/103(a) as unpatentable over McClelland *et al.* in view of Mullenbach *et al.*, and further in view of Akli *et al.* Claim 37 has been cancelled without prejudice and claims 36 and 38 have been amended in the instant amendment. Claims 36, 38, and 50 are pending in the instant application. Applicants respectfully traverse this rejection and submit that this combination of references fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

As discussed in Section 6 above, the combination of McClelland *et al.* and Mullenbach *et al.* fails to render obvious Applicants' claimed adenoviruses and cultured mammalian cells. Applicants submit that Akli *et al.* do not correct the deficiencies of McClelland *et al.* and Mullenbach *et al.*

Akli *et al.*

Akli *et al.* disclose the transfer of foreign genes into the brain using adenovirus vectors. In particular, Akli *et al.* teach the infection of a population of brain cells with an adenovirus encoding an *E. coli* lacZ marker gene, and expression of the gene in the brain for up to 45 days.

Akli *et al.* fail to correct the deficiencies of McClelland *et al.* and Mullenbach *et al.* identified above. In particular, Akli *et al.* fail to teach or suggest a replication defective recombinant adenovirus comprising a cDNA sequence encoding a human glutathione peroxidase. Absent such a disclosure, the combination of McClelland *et al.*, Mullenbach *et al.*, and Akli *et al.* cannot possibly render *prima facie* obvious the invention defined by any of Applicants' claims. Indeed, none of the references cited by the Examiner, either explicitly or implicitly, teach or suggest the invention defined by the present claims.

As discussed above, the combination of McClelland *et al.*, Mullenbach *et al.*, and Akli *et al.* simply does not suggest to one of ordinary skill in the art that Applicants' claimed invention could be achieved with a reasonable likelihood of success. Mullenbach *et al.* fail to provide any instructions or motivation to substitute their disclosed human glutathione peroxidase cDNA sequence for the therapeutic agent of McClelland *et al.* or to infect a cultured mammalian cell with such a replication defective recombinant adenovirus. Akli *et al.* fail to provide any instructions or motivation to substitute either their disclosed *E. coli* lacZ marker gene or the therapeutic agent of McClelland *et al.* with the cDNA

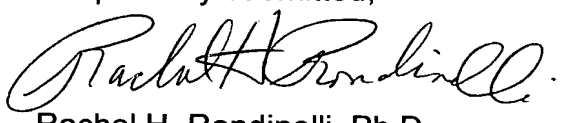
sequence encoding a human glutathione peroxidase of Mullenbach *et al.* or to infect a cultured mammalian cell with such a replication defective recombinant adenovirus.

Applicants submit that they were the first to suggest the adenoviruses and cultured mammalian cells claimed herein. As above, the combination of McClelland *et al.*, Mullenbach *et al.*, and Akli *et al.* is only possible using improper hindsight based on Applicants' disclosure. Accordingly, this rejection is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Favorable reconsideration and an action passing this case to issue are therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicants invite the Examiner to contact their attorney, Ross J. Oehler, at (610) 454-3883.

Respectfully submitted,



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